Specification

The Examiner has stated that the specification does not describe Figures 1B-1E on page 5. Applicants respectfully disagree. Applicants have provided the description of Figure 1, encompassing Figures 1A-1E in the Brief Description of the Drawings on page 5 of the instant specification, as well as in detail in Example 1 on pages 21-23. One skilled in the art understands that the description on page 5 and on pages 21-23 (Example 1), in combination with Figures 1A-1E, suggests that immunizing and boosting with two different vectors expressing the same TAA prolongs survival of tumor-bearing mice more efficiently than multiple immunizations with the same vector. Applicants respectfully request reconsideration and withdrawal of this objection.

35 U.S.C. §112

Claims 1-20 have been rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for obtaining an enhanced immune response using any combination of vectors as broadly claimed or treating cancer as claimed. Applicants respectfully disagree with this rejection.

The instant specification discloses a method for boosting an immunization using different vectors to deliver at least one gene of interest. Boosting takes the form of enhancing the immunological response an antigen can provide by changing the environment (i.e. the vector) in which it is delivered. The methods of the instant invention enhance the immunological response of existing gene therapies. Such gene therapy methods are not new to the artisan skilled in the field of gene-transfer immunotherapy. In fact, the first gene therapy was carried out more than ten years ago. A specification should not be burdened with information well-known to the skilled artisan.

More specifically, the Examiner has rejected claims 1-8 for not having an enabling use. The Examiner claims that the only disclosed purpose for enhancing an immune response in a

mammal using vectors encoding antigens is for the treatment of cancer, infectious disease, or autoimmune disease. Applicants respectfully disagree. However, in order to expedite prosecution of the application, applicants have amended independent claims 1 and 9.

Further, the Examiner points to claim 5 as not having an enabled use because inducing an immune response using a vector encoding an antigen and an immunostimulatory molecule is only disclosed for treating cancer. Examples of every possible embodiment of the invention need not be expressly set forth. Nevertheless, applicants respectfully direct the Examiner's attention to page 18, lines 11-25, which describes inducing an immune response using a vector encoding an antigen and an immunostimulatory molecule for diseases other than cancer, e.g. viral and fungal-related diseases. Also, as indicated on page 4, lines 2-13 of the instant specification, methods of enhancing an immune response in a mammal using vectors encoding antigens is enabled for treating cancer, infectious disease, or autoimmune disease. Therefore, the claimed invention has enabling uses for cancer, infectious disease, autoimmune disease, as well as for other uses, such as immunization procedures and other fungus- and virus- related diseases.

With respect to the combination of vectors for enhancing the immune response, the Examiner rejects the claims, because the specification allegedly does not provide adequate guidance. However, applicants respectfully disagree and direct the Examiner's attention to Example 2 and corresponding Figure 2. One skilled in the art can clearly see in Figure 2 and as described on page 25, Example 2, lines 6-29, that only those mice that are first primed with one vector (i.e., none, VJS6, FPV, DNA) and then boosted by another (i.e., VJS6, FPV) exhibited an effective immune response; for example, in FPV primed and VJS6 boosted, VJS6 primed and FPV boosted, or pCMV/βgal DNA primed followed by either boosting with VJS6 or FPV. Applicants assert that heterologous boosting as presently claimed is enabled by the instant specification where the second vector varies from the first vector and both vectors each contain nucleic acids encoding the same antigen. Applicants respectfully request reconsideration and withdrawal of the §112 rejection.

Further, claims 9-20 have been rejected as not being enabled because the specification allegedly does not provide adequate guidance to treat cancer using vectors encoding antigens as claimed. Applicants respectfully disagree with this rejection.

Applicants respectfully direct the Examiner's attention to the background section of the specification (pages 1-2) which describes the benefits and uses of vaccinia virus and fowlpox virus in vaccines. In particular, before the earliest priority date of the instant application, i.e. April 22, 1996, clinical studies using vaccinia virus were underway, as described by Cooney et al. and Graham et al. using recombinant vaccinia virus expressing the gp160 envelope gene of HIV and Estin et al. in phase I studies using recombinant vaccinia virus expressing the p97 melanoma antigen (page 1, line 29 through page 2, line 6). Therefore, the general concept of treating cancers using vectors encoding antigens is enabled in the art. The particular invention is enabled by the instant specification, for example, as described in the section entitled "Antigens Associated with Specific Diseases" on page 11, line 5 through page 13, line 19 and in Examples 4 and 5.

The Examiner has further concerns relating to targeting strategies. Applicants respectfully point to the summary of the invention which describes an antigen-specific immune response using two different recombinant vectors. One skilled in the art would understand that an antigen, specific for a tumor, such as a tumor-associated antigen (TAA), induces an immune response to that particular antigen against the tumor, for example. On page 9, line 19 through page 11, line 3, a general strategy for constructing recombinant vaccinia virus incorporating an exogenous gene, such as for example, a gene expressing a TAA inserted into the vector, is described in the specification. Also, Example 5 of the specification describes in detail one embodiment of the invention, the treatment of a melanoma patient with viral vectors expressing tumor associated antigens. Therefore, the claimed requirements of the invention relate to the use of at least two different vectors in which the antigen is presented. These requirements are described in detail in the instant specification. For these reasons, applicants respectfully disagree

with the Examiner's rejection and respectfully request reconsideration and withdrawal of the §112 rejection.

Claims 1-20 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully disagree with this rejection.

Specifically, the Examiner has stated that claim 1 is indefinite because the metes and bounds of an "enhanced immunological response" cannot be determined. The specification clearly demonstrates that the enhanced immunological response is a result of using at least two different vectors (i.e., heterologous) in the immunization process. Applicants respectfully direct the Examiner's attention to page 6, line 27 through page 7, line 3, and Example 1 on pages 21-23, where separately administering two different vaccination vectors having at least one similar tumor associated antigen enhances the immunological response. However, in order to address the Examiner's concerns, applicants have amended the claim.

Claims 1 and 9 have been rejected as being indefinite because the phrase "heterologous boosting immunization" is unclear. Specifically, it is allegedly unclear whether the term "heterologous" indicates the vectors that are foreign to the mammal, the vectors are different than each other, or the vectors have different effects on the immune system. Further, the Examiner is confused about the term "boosting," which in the Examiner's opinion, could be understood to occur when both vectors are administered or only after administration of the second vector. Applicants respectfully disagree with this rejection.

Applicants respectfully direct the Examiner's attention to pages 6-8, page 18, lines 26-33, and Example 1, where the phrase "heterologous boosting immunizations" specifically refers to a method for inducing an enhanced immunological response in a mammal by first inoculating the mammal with a recombinant vaccination vector and secondly, inoculating the mammal with a boosting immunization comprising a second recombinant vaccination vector different from the vector administered in the first step. The different vaccination vectors have at least one common antigen associated with a particular disease. Specifically, page 7, line 22 through page 8, line 5

of the specification describes "boosting" immunization as using a different vector from the priming dose of an antigen of the first step. Thus, "heterologous boosting immunization" means using at least two different vectors (i.e., heterologous), at least one for the priming dose and at least a second different vector for the follow-up (i.e., boosting) dose in order to obtain an enhanced or effective immunization. Applicants believe this definition of the phrase at issue is understood by the skilled artisan, based upon a reading of the instant specification. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner alleges that claim 1 is further indefinite in that "genes" do not necessarily encode "antigens." Applicants respectfully disagree, however in order to expedite prosecution, applicants have amended claim 1 to address the Examiner's concerns. Support may be found on page 8, lines 6-19 of the specification. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 5 and 14 are allegedly indefinite because it is unclear to the Examiner how the immunostimulatory molecule further limits the claim. The Examiner also alleges that it is unclear whether "immunostimulatory molecules" are limited to cytokines and co-stimulatory molecules or if the term encompasses antigens and viral proteins. The Examiner further alleges claims 5-14 to be indefinite because genes do not encode any "immunostimulatory molecule" as claimed. The Examiner suggests that the word "molecule" be changed to "protein" for clarity. Applicants respectfully disagree with this rejection.

Regarding the scope of the term "immunostimulatory molecules," the instant specification provides guidance on page 8, lines 6-35, wherein "immunostimulatory molecules" refers to antigens, tumor antigens, viral proteins, cytokines, restriction elements, co-stimulatory and accessory molecules.

In order to expedite prosecution of this application, applicants have amended claims 5-14 to replace "genes" with "nucleic acids" that encode immunostimulatory molecules. However, applicants maintain that the term "molecule" is correct as used in the claims and described in the specification. While it is true that not all "molecules" are proteins or peptides, it is also true that

all nucleic acids encoding "molecules," code for proteins or peptides. This fact is clear to one of ordinary skill in the art. Applicants respectfully request reconsideration and withdrawal of this §112 rejection.

Claim 9 has been rejected under 35 U.S.C. §112, second paragraph as being allegedly indefinite because mere administration of two vectors encoding antigen is not "treating said patient" as claimed. The Examiner believes that essential elements are missing from the claims and thus the claims are indefinite. Applicants respectfully disagree with this rejection.

In order to expedite prosecution, applicants have amended claim 9 to address the Examiner's concerns. Support may be found in the specification on page 7, lines 29-33, where "up-regulation of the immune response leads to an increase in antigen-specific cytotoxic lymphocytes which are able to kill or inhibit the growth of a disease-causing agent or a diseased cell." Additionally, the method of claim 9 may be used to enhance the immune response against the antigen associated with the disease, as described on page 8, lines 12-19 of the specification. Further, Example 1 describes the effects of first immunizing a subject with an effective amount of a first recombinant vector and then boosting the subject with an effective amount of a second recombinant vector. The resulting prolonged survival seen in the mice described in Example 1, demonstrates the efficacy of immunotherapy using the heterologous boosting immunization process claimed. Applicants respectfully request reconsideration and withdrawal of the §112 rejection.

35 U.S.C. §102

Claims 1-3, 5-7, 9, 14-16, 18 and 19 have been rejected under 35 U.S.C. §102(a) as being anticipated by Chamberlain et al. (April 20-24, 1996, *Proc. Ann. Meeting American Assoc. Cancer Res.*, Vol. 37, abstract 3263). Applicants respectfully disagree with this rejection.

The Chamberlain reference is an abstract from the proceedings of a meeting, which was published on March 21, 1996. The effective filing date of the instant application is April 22, 1996. Applicants assert that this abstract is not prior art under U.S. Patent law. In particular, 35

U.S.C §102(a) states that a person is entitled to a patent unless "the invention was known or used by others in this country or patented or described in a printed publication in this or a foreign country, *before the invention thereof by the applicant* for patent". The Chamberlain abstract is a publication by the applicants. To the extent that the abstract is relevant to the instant invention, the abstract itself is evidence that the invention was completed prior to the abstract's publication. Therefore, the Chamberlain abstract is not prior art under 35 U.S.C §102(a). Furthermore, Chamberlain is not prior art under 35 U.S.C. §102(b) because it was published less than one year prior to the filing date of the instant application. Applicants respectfully request reconsideration and withdrawal of this §102(a) rejection.

35 U.S.C. §103

Claims 1-3, 5-7, 9, 14-16, 18 and 19 have been rejected under 35 U.S.C.103(a) as being anticipated by Wang (J. Immunol., (1995 May 1) 154 (9): 4685-92). Applicants respectfully disagree with this rejection.

Wang describes using one vector, first alone, then with another vector having a nucleic acid encoding an antigen. This is different than the claimed invention which utilizes at least two different vectors each containing nucleic acids encoding at least one common antigen. As admitted by the Examiner, Wang does not teach administering vaccinia virus encoding β-gal followed by administering fowlpox virus encoding β-gal. Similarly, the Examiner further admits that Wang does not teach pre-immunizing with fowlpox virus encoding β-gal followed by administering vaccinia encoding β-gal. Applicants assert that it would not have been obvious to one skilled in the art to pre-immunize with one vector containing nucleic acids for an antigen followed by administering a second vector containing nucleic acids for the antigen from reading the Wang reference. In fact, the method described by Wang, i.e. first administering with either wild-type vaccinia virus alone or a control wild-type fowlpox virus alone (i.e., without a nucleic acid encoding an antigen), followed by vaccinations with either vaccinia virus expressing β-gal or fowlpox virus expressing β-gal, resulted in inhibition of the response against β-gal when wild-

type vaccinia virus was challenged with vaccinia virus expressing β-gal and did not diminish a response when challenged with fowlpox virus expressing β-gal. Therefore, one skilled in the art would have no motivation to modify or alter the experiment described in Figure 6 of the Wang reference to reach the present invention.

The skilled artisan reading the Wang reference would not be motivated to produce an immunological response to at least one antigen by inoculating with a first vector containing nucleic acids encoding the antigen and inoculating with a second vector containing the nucleic acids for the antigen in order to provide an effective immunological response, or in a cancer patient, to prolong survival using a TAA encoding nucleic acid. The cited Wang reference does not teach or suggest the use of different vectors in a single immunization protocol to deliver one or more antigens and produce an effective immunological response. Therefore, the cited prior art does not obviate the present invention.

Claim 5, which uses a recombinant vector comprising a nucleic acid encoding an immunostimulatory molecule in the method of claim 1, is also not taught or suggested by Wang. The Examiner alleges that since a vaccinia virus encodes proteins that are immunostimulatory and because β-gal is an immunostimulatory molecule, claim 5 is obvious. However, Wang does not teach or suggest the use of a vector in the claimed method which enhances an immunological response by innoculating the mammal with different vectors each containing at least one common nucleic acid encoding an antigen. Therefore, the applicants assert that it would not have been obvious for one reading the Wang reference to modify or alter its teachings in order to reach the present invention. Therefore, reconsideration and withdrawal of this §103 rejection is respectfully requested.

Claim 9, and thereby dependent claims 15 and 19, has been amended to include the therapeutic effect of prolonged patient survival as suggested by the Examiner. This amendment is supported throughout the specification and on page 19, lines 22-25, for example. Therefore,

the §103 rejection is believed to be overcome. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Claims 1-3, 5-7, 9-11, 14-16, 18 and 19 have been rejected under 35 U.S.C.103(a) as being anticipated by Wang (J. Immunol., (1995 May 1) 154 (9): 4685-92). Applicants respectfully disagree with this rejection.

As previously described, Wang does not teach or suggest the method of using different vectors containing a nucleic acid encoding at least one antigen. The Examiner further admits that Wang does not teach performing the method where β-gal is replaced with either MART-1 or gp100. Thus, Wang does not teach or suggest the claimed method of claims 1 and/or 9, nor does Wang provide any motivation to perform the claimed method using recombinant vectors comprising MART-1 or gp100 instead of β-gal. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Claims 1-3, 5-7, 9, 12-16, 18 and 19 have been rejected under 35 U.S.C.103(a) as being anticipated by Wang (J. Immunol., (1995 May 1) 154 (9): 4685-92) in view of Orlow (PNAS, Vol. 92:10152-10156, 1995). Applicants respectfully disagree with this rejection.

As previously described, Wang illustrates the use of fowlpox virus as a vector for carrying the β-gal gene. Orlow describes the changes in expression levels of four genes localized in melanosomes, the organelles in which melanin is synthesized. Neither of these references teach or suggest the use of different vectors having at least one of the same antigens for producing an effective immunological response. The skilled artisan reading these references would not be motivated to enhance an immunological response to at least one antigen by inoculating with a first recombinant vector containing a nucleic acid encoding the antigen and then inoculating with a second recombinant vector containing the nucleic acid for the antigen in order to produce an effective immunological response, or in a cancer patient, to prolong survival using a TAA-encoding nucleic acid. None of the cited prior art teaches or suggests the use of

different vectors to deliver one or more of the same antigens. Therefore, Wang, in view of Orlow, does not obviate the present invention. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Claims 1-9 and 14-20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154(9): 4685-92) in view of Zhai (Jan. 15, 1996, J. Immunol., 156(2):700-710).

Zhai describes the use of adenovirus as a vector for delivering genes encoding tumor antigens or models therefor to cells. Zhai does not teach or suggest the use of different vectors for boosting immunizations of at least one common antigen. The Wang reference does not teach or suggest the present invention as claimed. As previously discussed, Wang does not teach a method of administering different vectors having nucleic acids encoding at least one common antigen for inducing an effective immunological response raised against the antigen. Neither the Zhai reference or the Wang reference teach or suggest the concept of boosting immunization or prolonging survival of a cancer patient using different vectors and nucleic acids encoding at least one common antigen. This concept is not taught or suggested in any of the cited prior art. Therefore, the Wang and Zhai references, alone or in combination do not teach or suggest the use of different vectors in a heterologous boosting system to enhance immunological response or prolong survival in a patient. Therefore, applicants assert that the present invention is not obviated by the cited prior art. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

No additional fee is believed to be necessary.

Docket No. 2026-4231US3

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4231US3.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2026-4231US3. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Date: June 14, 2002

By: _____
Dorothy R. Auth
Registration No. 36,434

MORGAN & FINNEGAN, L.L.P.
345 Park Ave
New York, NY 10154-0053
(212)-758-4800 Telephone
(212)-751-6849 Facsimile

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VERSION WITH MARKINGS SHOWING CHANGES

Please amend the following claims:

1. (Twice amended) A method for immunizing a mammal against an antigen-associated disease inducing an effective immunological response against at least one antigen in the mammal using heterologous boosting immunization, said method comprising the steps of:

- inoculating the mammal with a first recombinant vector comprising a DNA vector and a nucleic acid [gene] encoding said antigen; and

- inoculating the mammal with a boosting immunization with a second recombinant vector comprising a second DNA vector and the nucleic acid [gene] encoding said antigen, wherein said second DNA vector is different from said first DNA vector, thereby inducing an effective immunological response thereby immunizing the mammal against the antigen-associated disease.

5. (twice amended) The method according to claim 1, wherein the recombinant vectors further comprise a nucleic acid [gene] encoding an immunostimulatory molecule.

9. (twice amended) A method for treatment of a cancer in a patient using heterologous boosting immunization as immunotherapy, said method comprising the steps of:

- immunizing said patient with an effective amount of a first recombinant vector comprising a first viral vector and a nucleic acid [gene] encoding a tumor-associated antigen; and

- boosting said patient with an effective amount of a second recombinant vector comprising a second viral vector and the nucleic acid [gene] encoding the tumor-associated antigen, wherein said second viral vector is different from said first viral vector, thereby treating said patient, to produce an effective immune response against the cancer in the patient.

14. (amended) The method according to claim 9, wherein the recombinant vectors further comprise a nucleic acid [gene] encoding an immunostimulatory molecule.